

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**21-223 /S004**

***Trade Name:*** Zometa

***Generic Name:*** (zoledronic acid) injection

***Sponsor:*** Novartis Pharmaceuticals Corporation

***Approval Date:*** March 7, 2003

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-223 /S004**

## CONTENTS

### Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-223 /S004**

**APPROVAL LETTER**



NDA 21-223/S-004

Novartis Pharmaceuticals Corporation  
Attention: Elizabeth McCartney  
Assistant Director, TRD/Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

Please refer to your supplemental new drug application dated June 20, 2002, received June 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We acknowledge receipt of your submissions dated October 1, 10, and 21, and November 6, 2002, and January 10, and 31, and February 10, and 19, 2003. Your submission of November 6, 2002 constituted a complete response to our October 18, 2002 action letter.

This supplemental new drug application provides for a liquid dosage form of the current lyophilized powder for reconstitution.

We have completed the review of this supplemental application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels submitted February 10, 2003) and must be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-223/S-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final

print. Submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HR-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Sheldon Markofsky, Ph.D.  
Acting Chemistry Team Leader II, DNDC II for the  
Division of Metabolic and Endocrine Drug Products  
Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Sheldon Markofsky  
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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

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**APPROVABLE LETTER**



NDA 21-223/S-004

Novartis Pharmaceuticals Corporation  
Attention: Elizabeth McCartney  
Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

Please refer to your supplemental new drug application dated June 20, 2002, received June 21, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We acknowledge receipt of your submissions dated July 9, and August 26, 2002.

We also acknowledge receipt of your submissions dated October 1 and 10, 2002. These submissions were not reviewed for the action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

This supplemental new drug application provides for a liquid dosage form of the current lyophilized powder for reconstitution.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Provide information on the components and composition of the ink and adhesives used on the proposed commercial label, and explain whether or not any other labels were used in any extraction or stability study.
2. Perform additional (accelerated) extraction studies on the drug product using the vial/stopper and the proposed commercial label. Look for any possible extractables/leachables using appropriate analytical methods (e.g. LC/MS).
3. Provide at least 6 month stability data using long-term conditions with the drug product and the proposed commercial label. 6 month stability data should be submitted, and relevant information about the size, ink and adhesive used should be clearly stated.
4. During a recent inspection of the packaging facility for this application, our field investigator conveyed deficiencies to the facility's representative.

Satisfactory resolution to these deficiencies is required before this application may be approved.

5. The reprocessing statement on page 794 states

In addition, you must submit draft labeling which addresses the following deficiencies:

1. The nonproprietary name is unacceptable. The name should be changed to
2. The proprietary name "Zometa"
3. The "preparation of solution" section of the draft package insert should include a statement indicating that when the diluted drug product is stored (for up to 24 hours) in the refrigerator, it has to be equilibrated to room temperature before administration.
4. Include the following statement (or similar wording) on the carton, and if possible on the vial label, "Not for direct injection"

Further, we have the following requests for information:

1. Monitoring of is done as part of the release and stability testing of the lyophilized powder.
2. Describe if particulate matter, mean mass, and sterility are monitored throughout the
3. Describe which tests in the stability protocol are conducted at the different time points.
4. Explain what means (Vol. 1, page 254).
5. The approved acceptance criteria for is not "NMT" but is "NMT". Therefore, the proposed acceptance criteria of "% " would expand the acceptance criteria. Please justify this expansion, or change the acceptance criteria.
6. Describe whether the manufacturing process of the drug product involves any reprocessing, aside from reprocessing. If so, described the reprocessing in detail.

7. The drug product specifications should include \_\_\_\_\_
8. The table in Vol. 1, on page 120, should be revised to provide for monitoring of particulate matter since the protocol provides for this monitoring.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Sheldon Markofsky, Ph.D.  
Acting Chemistry Team Leader II, DNDC II for the  
Division of Metabolic and Endocrine Drug Products  
Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Sheldon Markofsky  
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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**21-223/S004**

**LABELING**



T2002-xx  
XXXXXXXXXX

**Zometa<sup>®</sup>**  
**(zoledronic acid ) Injection**

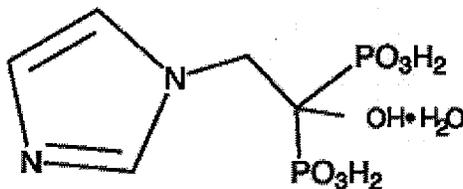
**Concentrate for Intravenous Infusion**

**Rx only**

**Prescribing Information**

**DESCRIPTION**

Zometa<sup>®</sup> contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is  $C_5H_{10}N_2O_7P_2 \cdot H_2O$  and its molar mass is 290.1g/Mol. Zoledronic acid is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Zometa<sup>®</sup> (zoledronic acid ) Injection is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5 ml vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis.

**Inactive Ingredients:** mannitol, USP, as bulking agent, water for injection and sodium citrate, USP, as buffering agent.

**CLINICAL PHARMACOLOGY**

**General**

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the

increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

## Pharmacokinetics

### *Distribution*

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg Zometa® were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of  $C_{max}$  24 hours post infusion with population half-lives of  $t_{1/2\alpha}$  0.24 hours and  $t_{1/2\beta}$  1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post infusion, and a terminal elimination half-life  $t_{1/2\gamma}$  of 146 hours. The area under the plasma concentration versus time curve ( $AUC_{0-24h}$ ) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean  $AUC_{0-24h}$  ratios for cycles 2 and 3 versus 1 of  $1.13 \pm 0.30$  and  $1.16 \pm 0.36$ , respectively.

*In vitro* and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 22% and was independent of the concentration of zoledronic acid.

### *Metabolism*

Zoledronic acid does not inhibit human P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi  $^{14}C$ -zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

### *Excretion*

In 64 patients with cancer and bone metastases on average ( $\pm$  s.d.)  $39 \pm 16\%$  of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was  $3.7 \pm 2.0$  L/h.

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study in patients with cancer and bone metastases, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid concentration at the end of the infusion ([mean  $\pm$  SD]  $403 \pm 118$  ng/mL vs  $264 \pm 86$  ng/mL) and a 10% increase in the total AUC (378

$\pm 116$  ng x h/mL vs  $420 \pm 218$  ng x h/mL). The difference between the AUC means was not statistically significant.

### Special Populations

Pharmacokinetic data in patients with hypercalcemia are not available.

**Pediatrics:** Pharmacokinetic data in pediatric patients are not available.

**Geriatrics:** The pharmacokinetics of zoledronic acid were not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

**Race:** The pharmacokinetics of zoledronic acid were not affected by race in patients with cancer and bone metastases.

**Hepatic Insufficiency:** No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

**Renal Insufficiency:** The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (N=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase in plasma AUC of 43%. Limited pharmacokinetic data are available for Zometa in patients with severe renal impairment (creatinine clearance <30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min.

Creatinine clearance is calculated by the Cockcroft-Gault formula (Creatinine clearance  $[CL_{cr}, \text{mL/min}] = [140 - \text{age}] * \text{weight [kg]} / X * [\text{plasma creatinine concentration}]$ , where  $X=72$  for males, and  $X=85$  for females]). Zometa systemic clearance in individual patients can be calculated from the population clearance of Zometa,  $CL (\text{L/h}) = 6.5(CL_{cr}/90)^{0.4}$ . These formulae can be used to predict the Zometa AUC in patients.  $CL = \text{Dose}/\text{AUC}$ . The average AUC in patients with normal renal function was  $0.42 \text{ mg} \cdot \text{h/L}$  (%CV 33) following a 4-mg dose of Zometa. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed. (See WARNINGS.)

### Pharmacodynamics

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

### Hypercalcemia of Malignancy

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This, in turn, results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcemia. Reducing

excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

Patients who have hypercalcemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcemia and hypercalcemia due to tumor invasion of bone. In humoral hypercalcemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumor and circulate systemically. Humoral hypercalcemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumors such as renal-cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumor cells can also result in hypercalcemia due to local tumor products that stimulate bone resorption by osteoclasts. Tumors commonly associated with locally mediated hypercalcemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels (corrected serum calcium, CSC) is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see DOSAGE AND ADMINISTRATION).

### Clinical Trials in Hypercalcemia of Malignancy

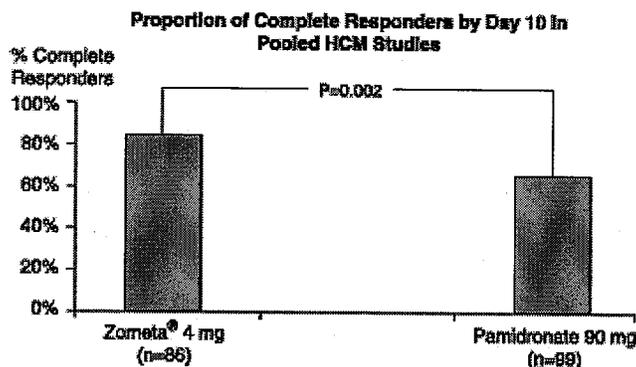
Two identical multicenter, randomized, double-blind, double-dummy studies of Zometa 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM). **NOTE: Administration of Zometa 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when Zometa 4 mg is given as a 15-minute intravenous infusion. Zometa should be administered by intravenous infusion over no less than 15 minutes. (See WARNINGS and DOSAGE AND ADMINISTRATION.)** The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The mean age of the study population was 59 years; 81% were Caucasian, 15% were Black, and 4% were of other races. Sixty percent of the patients were male. The most common tumor types were lung, breast, head and neck, and renal.

In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of  $\geq 12.0$  mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to  $\leq 10.8$  mg/dL (2.70 mmol/L) within 10 days after drug infusion.

To assess the effects of Zometa versus those of pamidronate, the two multicenter HCM studies were combined in a pre-planned analysis. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for Zometa 4 mg and pamidronate 90 mg, respectively (P=0.002).

(See Figure 1.) In these studies, no additional benefit was seen for Zometa 8 mg over Zometa 4 mg; however, the risk of renal toxicity of Zometa 8 mg was significantly greater than that seen with Zometa 4 mg.

Figure 1



Secondary efficacy variables from the pooled HCM studies included the proportion of patients who had normalization of corrected serum calcium (CSC) by Day 4; the proportion of patients who had normalization of CSC by Day 7; time to relapse of HCM; and duration of complete response. Time to relapse of HCM was defined as the duration (in days) of normalization of serum calcium from study drug infusion until the last CSC value <11.6 mg/dL (<2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC  $\leq$ 10.8 mg/dL (2.70 mmol/L). The results of these secondary analyses for Zometa 4 mg and pamidronate 90 mg are shown in Table 1.

Table 1: Secondary Efficacy Variables in Pooled HCM Studies

	Zometa® 4 mg		Pamidronate 90 mg	
	N	Response rate	N	Response rate
<b>Complete response</b>				
By Day 4	86	45.3%	99	33.3%
By Day 7	86	82.6%*	99	63.6%
<b>Duration of response</b>	N	Median duration (days)	N	Median duration (days)
Time to relapse	86	30*	99	17
Duration of complete response	76	32	69	18

\*P less than 0.05 vs. pamidronate 90 mg

### Clinical Trials in Multiple Myeloma and Bone Metastases of Solid Tumors

Table 2 describes three randomized Zometa trials in patients with multiple myeloma and bone metastases of solid tumors. These include a pamidronate-controlled study in breast cancer and multiple myeloma, a placebo-controlled study in prostate cancer and a placebo-controlled study in other solid tumors. The prostate cancer study required documentation of previous bone metastases and 3 consecutive rising PSAs while on hormonal therapy. The other

placebo-controlled solid tumor study included patients with bone metastases from malignancies other than breast cancer and prostate cancer, listed in Table 3.

**Table 2: Overview of Phase III Studies**

Study No.	No. of Patients	Treatment Duration	Zometa® Dose	Control	Patient Population
010	1648	12 months	4 and 8* mg Q3-4 weeks	Pamidronate 90 mg Q3-4 weeks	Multiple myeloma or metastatic breast cancer
039	643	15 months	4 and 8* mg Q3 weeks	Placebo	Metastatic prostate cancer
011	773	9 months	4 and 8* mg Q3 weeks	Placebo	Metastatic solid tumor other than breast or prostate cancer

\* Patients who were randomized to the 8-mg Zometa group are not included in any of the analyses in this package insert.

**Table 3: Solid Tumor Patients by Cancer Type and Treatment Arm**

Cancer type	Zometa® 4 mg	Placebo
	N	N
NSCLC	124	121
Renal	26	19
Small cell lung	19	22
Colorectal	19	16
Unknown	17	14
Bladder	11	16
GI (other)	10	12
Head and neck	6	4
Genitourinary	6	6
Malignant melanoma	5	4
Hepatobiliary	3	4
Thyroid	2	4
Other	3	2
Sarcoma	3	3
Neuroendocrine/carcinoid	2	3
Mesothelioma	1	0

The planned duration of therapy was 12 months for multiple myeloma and breast cancer, 15 months for prostate cancer, and 9 months for the other solid tumors.

The studies were amended twice because of renal toxicity. The Zometa infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8-mg Zometa treatment arm were switched to 4 mg. Patients who were randomized to the Zometa 8-mg group are not included in these analyses.

Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Change in antineoplastic therapy due to increased pain was a SRE in the prostate cancer study only. Planned analyses included the proportion of patients with a SRE during the study (the

primary endpoint) and time to first SRE. Results for the two Zometa placebo-controlled studies are given in Table 4.

**Table 4: Zometa® Compared to Placebo in Patients with Bone Metastases from Prostate Cancer or Other Solid Tumors**

Study	Study Arm	Analysis of Proportion of Patients with a SRE*			Analysis of Time to First SRE*			
		Proportion	Difference & 95% CI	P value	Median (days)	HR	95% CI of HR	P value
Prostate Cancer	Zometa 4 mg	33%	-11 (-20, -2)	0.021	NR	0.67	(0.49, 0.91)	0.011
	Placebo	44%	—	—	321	—	—	—
Solid Tumors	Zometa 4 mg	38%	-7 (-15, 2)	0.13	230	0.73	(0.55, 0.96)	0.023
	Placebo	44%	—	—	163	—	—	—

\*SRE = Skeletal Related Event

NR = Not reached by 420 days

HR = Hazard Ratio

In the breast cancer and myeloma trial, efficacy was determined by a non-inferiority analysis comparing Zometa to pamidronate 90 mg for the proportion of patients with a SRE. This analysis required an estimation of pamidronate efficacy. Historical data from 1128 patients in three pamidronate placebo-controlled trials demonstrated that pamidronate decreased the proportion of patients with a SRE by 13.1% (95% CI = 7.3%, 18.9%). Results of the comparison of treatment with Zometa compared to pamidronate are given in Table 5.

**Table 5: Zometa® Compared to Pamidronate in Patients with Multiple Myeloma or Bone Metastases from Breast Cancer**

Study	Study Arm	Analysis of Proportion of Patients with a SRE*			Analysis of Time to First SRE*			
		Proportion	Difference & 95% CI	P value	Median (days)	HR	95% CI of HR	P value
Multiple Myeloma and Breast Cancer	Zometa 4 mg	44%	-2 (-7.9, 3.7)	0.46	373	0.92	(0.77, 1.09)	0.322
	Pamidronate 90 mg	46%	—	—	363	—	—	—

\*SRE = Skeletal Related Event

HR = Hazard Ratio

## INDICATIONS AND USAGE

### Hypercalcemia of Malignancy

Zometa® (zoledronic acid ) Injection is indicated for the treatment of hypercalcemia of malignancy.

Vigorous saline hydration, an integral part of hypercalcemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day

throughout treatment. Mild or asymptomatic hypercalcemia may be treated with conservative measures (i.e., saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolemia. The safety and efficacy of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other non-tumor-related conditions has not been established.

### **Multiple Myeloma and Bone Metastases of Solid Tumors**

Zometa is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

### **CONTRAINDICATIONS**

Zometa<sup>®</sup> (zoledronic acid) Injection is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zometa.

### **WARNINGS**

**DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES.**

**BECAUSE SAFETY AND PHARMACOKINETIC DATA ARE LIMITED IN PATIENTS WITH SEVERE RENAL IMPAIRMENT:**

- **ZOMETA TREATMENT IS NOT RECOMMENDED IN PATIENTS WITH BONE METASTASES WITH SEVERE RENAL IMPAIRMENT.** In the clinical studies, patients with serum creatinine >3.0 mg/dL were excluded.
- **ZOMETA TREATMENT IN PATIENTS WITH HYPERCALCEMIA OF MALIGNANCY SHOULD BE CONSIDERED ONLY AFTER EVALUATING THE RISKS AND BENEFITS OF TREATMENT.** In the clinical studies, patients with serum creatinine >400 µmol/L or >4.5 mg/dL were excluded.

Bisphosphonates, including Zometa<sup>®</sup> (zoledronic acid) Injection, have been associated with renal toxicity manifested as deterioration of renal function and potential renal failure. In clinical trials, the risk for renal function deterioration (defined as an increase in serum creatinine) was significantly increased in patients who received Zometa over 5 minutes compared to patients who received the same dose over 15 minutes. In addition, the risk for renal function deterioration and renal failure was significantly increased in patients who received Zometa 8 mg, even when given over 15 minutes. While this risk is reduced with the Zometa 4-mg dose administered over 15 minutes, deterioration in renal function can still

occur. Risk factors for this deterioration include elevated baseline creatinine and multiple cycles of treatment with the bisphosphonate.

Patients who receive Zometa should have serum creatinine assessed prior to each treatment. Patients treated with Zometa for bone metastases should have the dose withheld if renal function has deteriorated. (See DOSAGE AND ADMINISTRATION.) Patients with hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk.

**PREGNANCY: ZOMETA SHOULD NOT BE USED DURING PREGNANCY.** Zometa may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure (an i.v. dose of 4 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. (See PRECAUTIONS, Pregnancy Category D.)

There are no studies in pregnant women using Zometa. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

## PRECAUTIONS

### General

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with Zometa® (zoledronic acid) Injection. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to administration of Zometa. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with Zometa in order to avoid hypocalcemia. Zometa should be used with caution with other nephrotoxic drugs.

**Renal Insufficiency:** Limited clinical data are available regarding use of Zometa in patients with renal impairment. Zometa is excreted intact primarily via the kidney, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Serum creatinine should be monitored in all patients treated with Zometa prior to each dose.

Studies of Zometa in the treatment of hypercalcemia of malignancy excluded patients with serum creatinine  $\geq 400$   $\mu\text{mol/L}$  or  $\geq 4.5$   $\text{mg/dL}$ . Bone metastasis trials excluded patients with serum creatinine  $> 265$   $\mu\text{mol/L}$  or  $> 3.0$   $\text{mg/dL}$ . No clinical or pharmacokinetics data are available to guide dose selection or to provide guidance on how to safely use Zometa in patients with severe renal impairment. For hypercalcemia of malignancy, Zometa should be used in patients with severe renal impairment only if the expected clinical benefits outweigh the risk of renal failure and after considering other available treatment options. (See WARNINGS.) Dose adjustments of Zometa are not necessary in treating patients for

hypercalcemia presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400  $\mu\text{mol/L}$  or <4.5 mg/dL). For bone metastases, the use of Zometa in patients with severe renal impairment is not recommended. In studies of patients with bone metastases, patients with a serum creatinine >3.0 mg/dL were excluded.

Patients receiving Zometa for hypercalcemia of malignancy with evidence of deterioration in renal function should be appropriately evaluated and consideration should be given as to whether the potential benefit of continued treatment with Zometa outweighs the possible risk. In patients receiving Zometa for bone metastases, who show evidence of deterioration in renal function, Zometa treatment should be withheld until renal function returns to baseline. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

**Hepatic Insufficiency:** Only limited clinical data are available for use of Zometa to treat hypercalcemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use Zometa in these patients.

**Patients with Asthma:** While not observed in clinical trials with Zometa, administration of other bisphosphonates has been associated with bronchoconstriction in aspirin-sensitive asthmatic patients. Zometa should be used with caution in patients with aspirin-sensitive asthma.

### Laboratory Tests

Serum creatinine should be monitored prior to each dose of Zometa. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly. (See WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS.)

### Drug Interactions

*In vitro* studies indicate that zoledronic acid is approximately 56% bound to plasma proteins. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug. However, no *in vivo* drug interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This has not been reported in Zometa clinical trials. Caution should also be exercised when Zometa is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when Zometa is used with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zometa is used in combination with thalidomide.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

**Carcinogenesis:** Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was

an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses  $\geq 0.002$  times a human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed (at doses  $\leq 0.2$  times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas).

**Mutagenesis:** Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

**Impairment of Fertility:** Female rats were given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group (with systemic exposure of 0.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and high-dose group included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

#### **Pregnancy Category D See WARNINGS.**

In female rats given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day beginning 15 days before mating and continuing through gestation, the number of stillbirths was increased and survival of neonates was decreased in the mid- and high-dose groups ( $\geq 0.2$  times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Adverse maternal effects were observed in all dose groups (with a systemic exposure of  $\geq 0.07$  times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison) and included dystocia and periparturient mortality in pregnant rats allowed to deliver. Maternal mortality may have been related to drug-induced inhibition of skeletal calcium mobilization, resulting in periparturient hypocalcemia. This appears to be a bisphosphonate class effect.

In pregnant rats given a subcutaneous dose of zoledronic acid of 0.1, 0.2, or 0.4 mg/kg/day during gestation, adverse fetal effects were observed in the mid- and high-dose groups (with systemic exposures of 2.4 and 4.8 times, respectively, the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). These adverse effects included increases in pre- and post-implantation losses, decreases in viable fetuses, and fetal skeletal, visceral, and external malformations. Fetal skeletal effects observed in the high-dose group included unossified or incompletely ossified bones, thickened, curved or shortened bones, wavy ribs, and shortened jaw. Other adverse fetal effects observed in the high-dose group included reduced lens, rudimentary cerebellum, reduction or absence of liver lobes, reduction of lung lobes, vessel dilation, cleft palate, and edema. Skeletal variations were also observed in the low-dose group (with systemic exposure of 1.2 times the human systemic exposure following an intravenous dose of 4 mg, based on an AUC comparison). Signs of maternal toxicity were observed in the high-dose group and included reduced body weights and food consumption, indicating that maximal exposure levels were achieved in this study.

In pregnant rabbits given subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg/day during gestation ( $\leq 0.5$  times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas), no adverse fetal effects were observed. Maternal mortality and abortion occurred in all treatment groups (at doses  $\geq 0.05$  times the human intravenous dose of 4 mg, based on a comparison of relative body surface areas). Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

### **Nursing Mothers**

It is not known whether Zometa is excreted in human milk. Because many drugs are excreted in human milk, and because Zometa binds to bone long-term, Zometa should not be administered to a nursing woman.

### **Pediatric Use**

The safety and effectiveness of Zometa in pediatric patients have not been established. Because of long-term retention in bone, Zometa should only be used in children if the potential benefit outweighs the potential risk.

### **Geriatric Use**

Clinical studies of Zometa in hypercalcemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving Zometa as compared to younger patients. Controlled clinical studies of Zometa in the treatment of multiple myeloma and bone metastases of solid tumors in patients over age 65 revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

## **ADVERSE REACTIONS**

### **Hypercalcemia of Malignancy**

Adverse reactions to Zometa<sup>®</sup> (zoledronic acid) Injection are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with fever. Occasionally, patients experience a flu-like syndrome consisting of fever, chills, bone pain and/or arthralgias, and myalgias. Gastrointestinal reactions such as nausea and vomiting have been reported following intravenous infusion of Zometa. Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Rare cases of rash, pruritus, and chest pain have been reported following treatment with Zometa.

As with other bisphosphonates, cases of conjunctivitis and hypomagnesemia have been reported following treatment with Zometa.

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in two clinical trials of Zometa in patients with HCM are shown in Table 6.

**Table 6: Grade 3-4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Two Clinical Trials In Patients with HCM.**

Laboratory Parameter	Grade 3				Grade 4			
	Zometa® 4 mg		Pamidronate 90 mg		Zometa® 4 mg		Pamidronate 90 mg	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine <sup>1</sup>	2/86	(2.3%)	3/100	(3.0%)	0/86	---	1/100	(1.0%)
Hypocalcemia <sup>2</sup>	1/86	(1.2%)	2/100	(2.0%)	0/86	---	0/100	---
Hypophosphatemia <sup>3</sup>	36/70	(51.4%)	27/81	(33.3%)	1/70	(1.4%)	4/81	(4.9%)
Hypomagnesemia <sup>4</sup>	0/71	---	0/84	---	0/71	---	1/84	(1.2%)

<sup>1</sup>Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)

<sup>2</sup>Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)

<sup>3</sup>Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)

<sup>4</sup>Grade 3 (<0.8 mEq/L); Grade 4 (<0.5 mEq/L)

Table 7 provides adverse events that were reported by 10% or more of the 189 patients treated with Zometa 4 mg or pamidronate 90 mg from the two controlled multi-center HCM trials. Adverse events are listed regardless of presumed causality to study drug.

**Table 7: Percentage of Patients with Adverse Events ≥10% Reported in Hypercalcemia of Malignancy Clinical Trials By Body System**

	Zometa® 4 mg n (%)	Pamidronate 90 mg n (%)
<b>Patients Studied</b>		
Total no. of patients studied	86 (100)	103 (100)
Total no. of patients with any AE	81 (94.2)	95 (92.2)
<b>Body as a Whole</b>		
Fever	38 (44.2)	34 (33.0)
Progression of Cancer	14 (16.3)	21 (20.4)
<b>Digestive</b>		
Nausea	25 (29.1)	28 (27.2)
Constipation	23 (26.7)	13 (12.6)
Diarrhea	15 (17.4)	17 (16.5)
Abdominal Pain	14 (16.3)	13 (12.6)
Vomiting	12 (14.0)	17 (16.5)
Anorexia	8 (9.3)	14 (13.6)
<b>Cardiovascular</b>		
Hypotension	9 (10.5)	2 (1.9)
<b>Hemic and Lymphatic System</b>		
Anemia	19 (22.1)	18 (17.5)
<b>Infections</b>		
Moniliasis	10 (11.6)	4 (3.9)
<b>Laboratory Abnormalities</b>		
Hypophosphatemia	11 (12.8)	2 (1.9)
Hypokalemia	10 (11.6)	16 (15.5)
Hypomagnesemia	9 (10.5)	5 (4.9)
<b>Musculoskeletal</b>		
Skeletal Pain	10 (11.6)	10 (9.7)
<b>Nervous</b>		
Insomnia	13 (15.1)	10 (9.7)
Anxiety	12 (14.0)	8 (7.8)
Confusion	11 (12.8)	13 (12.6)
Agitation	11 (12.8)	8 (7.8)
<b>Respiratory</b>		
Dyspnea	19 (22.1)	20 (19.4)
Coughing	10 (11.6)	12 (11.7)
<b>Urogenital</b>		
Urinary Tract Infection	12 (14.0)	15 (14.6)

The following adverse events from the two controlled multi-center HCM trials (n=189) were reported by a greater percentage of patients treated with Zometa 4 mg than with pamidronate 90 mg and occurred with a frequency of greater than or equal to 5% but less than 10%. Adverse events are listed regardless of presumed causality to study drug.

**Body as a Whole:** asthenia, chest pain, leg edema, mucositis, metastases

**Digestive System:** dysphagia

**Hemic and Lymphatic System:** granulocytopenia, thrombocytopenia, pancytopenia

**Infection:** non-specific infection

**Laboratory Abnormalities:** hypocalcemia

**Metabolic and Nutritional:** dehydration

**Musculoskeletal:** arthralgias

**Nervous System:** headache, somnolence

**Respiratory System:** pleural effusion

**NOTE:** In the HCM clinical trials, pamidronate 90 mg was given as a 2-hour intravenous infusion. The relative safety of pamidronate 90 mg given as a 2-hour intravenous infusion compared to the same dose given as a 24-hour intravenous infusion has not been adequately studied in controlled clinical trials.

### **Multiple Myeloma and Bone Metastases of Solid Tumors**

Table 8 provides adverse events that were reported by 10% or more of the 2185 patients treated with Zometa 4 mg, pamidronate 90 mg or placebo from the four controlled multi-center Bone Metastases trials. Adverse events are listed regardless of presumed causality to study drug.

**Table 8: Percentage of Patients with Adverse Events ≥10% Reported in Four Bone Metastases Clinical Trials By Body System**

	<b>Zometa® 4 mg n (%)</b>	<b>Pamidronate 90 mg n (%)</b>	<b>Placebo n (%)</b>
<b>Patients Studied</b>			
Total no. of patients	1099 (100)	631 (100)	455 (100)
Total no. of patients with any AE	1081 (98)	622 (99)	444 (98)
<b>Blood and Lymphatic</b>			
Anemia	320 (29)	170 (27)	119 (26)
Neutropenia	121 (11)	87 (14)	34 (8)
<b>Gastrointestinal</b>			
Nausea	470 (43)	282 (45)	160 (35)
Vomiting	328 (30)	189 (30)	114 (25)
Constipation	307 (28)	148 (24)	161 (35)
Diarrhea	238 (22)	157 (25)	76 (17)
Abdominal Pain	128 (12)	70 (11)	43 (10)
<b>General Disorders and Administration Site</b>			
Fatigue	394 (36)	235 (37)	125 (28)
Pyrexia	326 (30)	175 (28)	83 (18)
Weakness	232 (21)	103 (16)	105 (23)
Edema Lower Limb	203 (19)	115 (18)	76 (17)
Rigors	107 (10)	64 (10)	21 (5)
<b>Infections</b>			
Urinary Tract Infection	115 (11)	53 (8)	39 (9)
Upper Respiratory Tract Infection	88 (8)	83 (13)	26 (6)
<b>Metabolism</b>			
Anorexia	220 (20)	76 (12)	98 (22)
Weight Decreased	143 (13)	45 (7)	57 (13)
Dehydration	135 (12)	57 (9)	54 (12)
Appetite Decreased	119 (11)	46 (7)	39 (9)

<b>Musculoskeletal</b>			
Bone Pain	579 (53)	345 (55)	272 (60)
Myalgia	232 (21)	148 (24)	68 (15)
Arthralgia	195 (18)	109 (17)	60 (13)
Back Pain	113 (10)	79 (13)	29 (6)
<b>Neoplasms</b>			
Malignant Neoplasm Aggravated	166 (15)	71 (11)	72 (16)
<b>Nervous</b>			
Headache	193 (18)	152 (24)	47 (10)
Dizziness (excluding vertigo)	158 (14)	79 (13)	52 (11)
Insomnia	154 (14)	106 (17)	67 (15)
Paresthesia	129 (12)	85 (14)	28 (6)
Hypoesthesia	109 (10)	63 (10)	38 (8)
<b>Psychiatric</b>			
Depression	136 (12)	89 (14)	41 (9)
Anxiety	101 (9)	76 (12)	34 (8)
<b>Respiratory</b>			
Dyspnea	264 (24)	147 (23)	93 (20)
Cough	212 (19)	132 (21)	57 (13)
<b>Skin</b>			
Alopecia	119 (11)	83 (13)	30 (7)
Dermatitis	108 (10)	68 (11)	35 (8)

Grade 3 and Grade 4 laboratory abnormalities for serum creatinine, serum calcium, serum phosphorus, and serum magnesium observed in four clinical trials of Zometa in patients with Bone Metastases are shown in Tables 9 and 10.

**Table 9: Grade 3 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Four Clinical Trials in Patients with Bone Metastases**

Laboratory Parameter	Grade 3					
	Zometa® 4 mg		Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine <sup>1*</sup>	7/529	(1.3%)	4/268	(1.5%)	2/241	(0.8%)
Hypocalcemia <sup>2</sup>	7/1041	(0.7%)	4/610	(0.7%)	0/415	—
Hypophosphatemia <sup>3</sup>	96/1041	(9.2%)	40/611	(6.6%)	13/415	(3.1%)
Hypermagnesemia <sup>4</sup>	19/1039	(1.8%)	3/609	(0.5%)	8/415	(1.9%)
Hypomagnesemia <sup>5</sup>	0/1039	—	0/609	—	1/415	(0.2%)

<sup>1</sup> Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)

\* Serum creatinine data for all patients randomized after the 15-minute infusion amendment

<sup>2</sup> Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)

<sup>3</sup> Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)

<sup>4</sup> Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)

<sup>5</sup> Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

**Table 10: Grade 4 Laboratory Abnormalities for Serum Creatinine, Serum Calcium, Serum Phosphorus, and Serum Magnesium in Four Clinical Trials in Patients with Bone Metastases**

Laboratory Parameter	Grade 4					
	Zometa® 4 mg		Pamidronate 90 mg		Placebo	
	n/N	(%)	n/N	(%)	n/N	(%)
Serum Creatinine <sup>1*</sup>	2/529	(0.4%)	1/268	(0.4%)	0/241	—
Hypocalcemia <sup>2</sup>	6/1041	(0.6%)	2/610	(0.3%)	1/415	(0.2%)
Hypophosphatemia <sup>3</sup>	6/1041	(0.6%)	0/611	—	1/415	(0.2%)
Hypermagnesemia <sup>4</sup>	0/1039	—	0/609	—	2/415	(0.5%)
Hypomagnesemia <sup>5</sup>	2/1039	(0.2%)	2/609	(0.3%)	0/415	—

<sup>1</sup> Grade 3 (>3x Upper Limit of Normal); Grade 4 (>6x Upper Limit of Normal)

\* Serum creatinine data for all patients randomized after the 15-minute infusion amendment

<sup>2</sup> Grade 3 (<7 mg/dL); Grade 4 (<6 mg/dL)

<sup>3</sup> Grade 3 (<2 mg/dL); Grade 4 (<1 mg/dL)

<sup>4</sup> Grade 3 (>3 mEq/L); Grade 4 (>8 mEq/L)

<sup>5</sup> Grade 3 (<0.9 mEq/L); Grade 4 (<0.7 mEq/L)

Among the less frequently occurring adverse events (<15% of patients), rigors, hypokalemia, influenza-like illness, and hypocalcemia showed a trend for more events with bisphosphonate administration (Zometa 4 mg and pamidronate groups) compared to the placebo group.

Less common adverse events reported more often with Zometa 4 mg than pamidronate included decreased weight, which was reported in 13.0% of patients in the Zometa 4 mg compared with 7.1% in the pamidronate group. The incidence of decreased weight, however, was similar for the placebo group (12.5%) and Zometa. Decreased appetite was reported in slightly more patients in the Zometa 4 mg (10.8%) compared with the pamidronate (7.3%) and placebo (8.6%) groups, but the clinical significance of these small differences is not clear.

## Renal Toxicity

In the bone metastases trials renal deterioration was defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (<1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (≥1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving Zometa 4 mg over 15 minutes in these trials. (See Table 11.)

**Table 11: Percentage of Patients with Renal Function Deterioration Who Were Randomized Following the 15-Minute Infusion Amendment**

Patient Population/Baseline Creatinine	Zometa® 4 mg		Pamidronate 90 mg	
	n/N	(%)	n/N	(%)
Multiple Myeloma and Breast Cancer				
Normal	23/246	(9.3%)	20/246	(8.1%)
Abnormal	1/26	(3.8%)	2/22	(9.1%)
Total	24/272	(8.8%)	22/268	(8.2%)

Solid Tumors	Zometa® 4 mg		Placebo	
	n/N	(%)	n/N	(%)
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9.1%)	1/20	(5%)
Total	18/165	(10.9%)	11/163	(6.7%)

Prostate Cancer	Zometa® 4 mg		Placebo	
	n/N	(%)	n/N	(%)
Normal	10/82	(12.2%)	7/68	(10.3%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	14/92	(15.2%)	9/78	(11.5%)

The risk of deterioration in renal function appeared to be related to time on study, whether patients were receiving Zometa (4 mg over 15 minutes), placebo, or pamidronate.

## OVERDOSAGE

There is no experience of acute overdose with Zometa® (zoledronic acid) Injection. Two patients received Zometa 32 mg over 5 minutes in clinical trials. Neither patient experienced any clinical or laboratory toxicity. Overdosage may cause clinically significant hypocalcemia, hypophosphatemia, and hypomagnesemia. Clinically relevant reductions in serum levels of calcium, phosphorus, and magnesium should be corrected by intravenous administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulfate, respectively.

In controlled clinical trials, administration of Zometa 4 mg as an intravenous infusion over 5 minutes has been shown to increase the risk of renal toxicity compared to the same dose administered as a 15-minute intravenous infusion. In controlled clinical trials, Zometa 8 mg has been shown to be associated with an increased risk of renal toxicity compared to Zometa 4 mg, even when given as a 15-minute intravenous infusion, and was not associated with added benefit in patients with hypercalcemia of malignancy. **Single doses of Zometa should not exceed 4 mg and the duration of the intravenous infusion should be no less than 15 minutes. (See WARNINGS.)**

## DOSAGE AND ADMINISTRATION

### Hypercalcemia of Malignancy

Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zometa® (zoledronic acid) Injection. Vigorous saline hydration alone may be sufficient to treat mild, asymptomatic hypercalcemia.

The maximum recommended dose of Zometa in hypercalcemia of malignancy (albumin-corrected serum calcium\*  $\geq 12$  mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over **no less than 15 minutes**.

Patients should be adequately rehydrated prior to administration of Zometa. (See WARNINGS and PRECAUTIONS.)

Retreatment with Zometa 4 mg, may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days

elapse before retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zometa and possible deterioration in renal function must be assessed prior to retreatment with Zometa. (See WARNINGS and PRECAUTIONS.)

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\*Albumin-corrected serum calcium (Cca, mg/dL) =  $Ca + 0.8$  (mid-range albumin-measured albumin in mg/dL).

### **Multiple Myeloma and Metastatic Bone Lesions From Solid Tumors**

The recommended dose of Zometa in patients with multiple myeloma and metastatic bone lesions from solid tumors is 4 mg infused over 15 minutes every three or four weeks. Duration of treatment in the clinical studies was 15 months for prostate cancer, 12 months for breast cancer and multiple myeloma, and 9 months for other solid tumors. Patients should also be administered an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily.

Serum creatinine should be measured before each Zometa dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine, increase of 0.5 mg/dL
- For patients with abnormal baseline creatinine, increase of 1.0 mg/dL

In the clinical studies, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value.

### **Preparation of Solution**

Vials of Zometa concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. The dose must be given as a single intravenous infusion over no less than 15 minutes.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 36°F-46°F (2°C-8°C). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours

**Zometa must not be mixed with calcium-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.**

***Method of Administration:* DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOMETA SHOULD NOT EXCEED 4 MG AND THE**

**DURATION OF INFUSION SHOULD BE NO LESS THAN 15 MINUTES. (SEE WARNINGS.)**

There must be strict adherence to the intravenous administration recommendations for Zometa in order to decrease the risk of deterioration in renal function.

**Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

**HOW SUPPLIED**

Each 5 ml vial contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection and 24 mg of sodium citrate, USP.

Carton of 1 vial..... NDC 0078-0387-25

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

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■ PMS 273

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1 vial Sterile Concentrate  
Concentrate for  
Intravenous Infusion  
**4 mg/5 mL**

**Zometa®  
(zoledronic acid)  
Injection**

See package insert  
for DOSAGE and  
ADMINISTRATION and  
Preparation of Solution.

Each vial delivers zoledronic  
acid monohydrate 4.264 mg  
(equivalent to 4 mg zoledronic  
acid on an anhydrous basis),  
mannitol, USP 220 mg, water  
for injection and sodium citrate  
to adjust pH.

The pH of the concentrate is  
5.7-6.7.

Zometa diluted with infusion  
media, may be stored under  
refrigeration at 2°C-8°C  
(36°F-46°F).

Total time between dilution  
with infusion media and end  
of administration must not  
exceed 24 hours.

Store at 25°C (77°F);  
excursions permitted to  
15°C-30°C (59°F-86°F).



NDC 0078-0387-25

**Zometa®  
(zoledronic acid)  
Injection**

**4 mg/5 mL**  
Concentrate for  
Intravenous Infusion  
1 vial Sterile Concentrate

**Not for direct injection.  
Dose must be diluted.  
See package insert for  
Preparation of Solution.  
Do not mix with calcium-  
containing infusion solutions.**

Rx only



Manufactured by  
Novartis Pharma Stein AG  
Stein, Switzerland for  
Novartis Pharmaceuticals  
Corporation  
East Hanover, NJ 07936

©Novartis

Reflex Blue  
PMS 314

Do not mix with  
calcium-containing  
infusion solutions.  
Store at 25°C (77°F);  
excursions permitted to  
15°-30°C (59°-86°F).  
Rx only 80051701

NDC 0078-0387-25

**Zometa®**

(zoledronic acid) Injection

Concentrate for

Intravenous Infusion

**4 mg/5 mL**

US

Manufactured by  
Novartis Pharma Stein AG  
Novartis Pharma Stein  
Novartis Pharma Corp.  
E. Hanover, NJ 07936  
484185

EXP/LOT

1:1

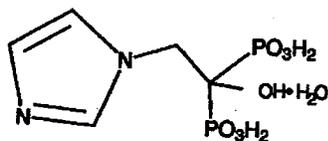
**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-223 /S004**

**CHEMISTRY REVIEW(S)**

<b>CHEMIST'S REVIEW</b>	1. ORGANIZATION	2. NDA NUMBER
	DMEDP, HFD-510	21-223
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Novartis Pharmaceutical Corporation 59 Route 10 East Hanover, NJ 07936-1080		SCF-004, (PA) 11/6/02 User Fee date: 3/7/03 (4 months)
5. NAME OF THE DRUG	6. NONPROPRIETARY NAME	
Zometa®	Zoledronic acid injection	
7. SUPPLEMENT PROVIDES FOR:		8. AMENDMENTS/REPORT, DATE
A complete response to the original supplement that provided for the addition of a new concentrated liquid dosage form along with a new container closure system and new labeling.		10/1/02 10/10/02 1/10/03 2/14/03 3/3/03 3/4/03
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND/NDA/DMF
Inhibitor of bone resorption	R <sub>x</sub>	DMF
12. DOSAGE FORM	13. POTENCY	
Injection	4 mg/vial	
14. CHEMICAL NAME AND STRUCTURE.		
(1-Hydroxy-2-imidazol-1-yl-phosphonoethyl)phosphonic acid monohydrate		



15. COMMENTS		
<p>This original supplement was submitted as a PA supplement to HFD-510. The supplement provides for the addition of a concentrated liquid (4 mg/5 mL) of the drug product, which is currently only available (and approved) as a lyophilized powder. A new container closure system and new labeling are proposed for the new dosage form. The amendment dated 10/1/02 provides for a response to an information request letter from the Agency dated 9/13/02. The amendment dated 10/10/02 provides for a response to an information request (telephone call on 10/1/02) regarding which labels were used in the extraction studies. An approvable letter, dated 10/18/02 was sent to the sponsor. This review covers the complete response (amendment dated 11/6/02) to all chemistry deficiencies, labeling deficiencies and requests for information, noted in the 10/18/02 letter. The amendment dated 1/10/03 provides for the sponsor's position regarding the trade name Zometa. The amendment dated 2/14/03 provides a letter of authorization to refer to DMF. The amendment dated 3/3/03 contains additional information about the paper used for the vial label. The amendment dated 3/4/03 contains a response to questions regarding the chromatograms obtained in the extraction study.</p>		
16. CONCLUSION AND RECOMMENDATION		
Adequate information has been provided. This supplement can be approved. Issue an approval letter.		
17. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Elsbeth G. Chikhale, Ph.D.		3/4/03
DISTRIBUTION:	ORIGINAL JACKET	CSO REVIEWER DIVISION FILE

Init. by:

CC: HFD-510; NDA 21-223/S-004.  
HFD-510: S Markofsky /R Hedin/ EG Chikhale  
Division file/NDA 21-223.

**Appears This Way  
On Original**

10 Page(s) Withheld

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Confidential

       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

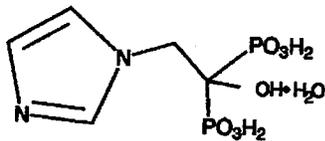
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/s/

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Elsbeth Chikhale  
3/4/03 03:04:53 PM  
CHEMIST

Sheldon Markofsky  
3/4/03 03:18:30 PM  
CHEMIST

<b>CHEMIST'S REVIEW</b>		1. ORGANIZATION DMEDP, HFD-510	2. NDA NUMBER 21-223
3. NAME AND ADDRESS OF APPLICANT Novartis Pharmaceutical Corporation 59 Route 10 East Hanover, NJ 07936-1080		4. SUPPLEMENT NUMBER, DATE SCF-004, (PA) 6/20/02 User Fee date: 10/21/02 (4 months)	
5. NAME OF THE DRUG Zometa®	6. NONPROPRIETARY NAME Zoledronic acid injection		
7. SUPPLEMENT PROVIDES FOR: Addition of a new concentrated liquid dosage form along with a new container closure system and new labeling.		8. AMENDMENTS/REPORT, DATE Fax 7/9/02 8/26/02	
9. PHARMACOLOGICAL CATEGORY Inhibitor of bone resorption	10. HOW DISPENSED Rx	11. RELATED IND/NDA/DMF DMF —	
12. DOSAGE FORM Injection	13. POTENCY 4 mg/vial		DMF —
14. CHEMICAL NAME AND STRUCTURE. (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl)phosphonic acid monohydrate			



15. COMMENTS		
<p>This supplement is submitted as a PA supplement to HFD-510. The supplement provides for the addition of a concentrated liquid (4 mg/5 mL) of the drug product, which is currently only available (and approved) as a lyophilized powder. A new container closure system and new labeling are proposed for the new dosage form. The fax dated 7/9/02 and the amendment dated 8/26/02 both provide responses to information request phone calls from the Agency on 7/2/02 and 7/11/02, concerning extractables or leachables from the proposed container closure system. The amendment (8/26/02) also contains questions to the Agency, regarding extractables or leachables from the proposed container closure system, which were answered in a letter from the Agency dated 9/13/02. An amendment dated 10/1/02, provides additional information in response to Agency's telephone call on 7/11/02 and letter dated 9/13/02. It also contains additional stability data. However, this amendment, dated 10/1/02, and another amendment dated 10/10/02, could not be reviewed because it came in too late in the review cycle.</p>		
16. CONCLUSION AND RECOMMENDATION		
<p>The CMC information is inadequate. This supplement is approvable pending resolution of the deficiencies and pending an acceptable cGMP status from all of the relevant facilities. See draft list of deficiencies.</p>		
17. NAME Elsbeth G. Chikhale, Ph.D.	REVIEWER SIGNATURE	DATE COMPLETED 10/16/02
DISTRIBUTION:	ORIGINAL JACKET	CSO REVIEWER DIVISION FILE

Init. by:  
 CC: HFD-510; NDA 21-223/S-004.  
 HFD-510: S Markofsky /R Hedin/ EG Chikhale  
 Division file/NDA 21-223.

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       § 552(b)(5) Deliberative Process

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/s/

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Elsbeth Chikhale  
10/16/02 01:21:46 PM  
CHEMIST

Sheldon Markofsky  
10/16/02 01:54:09 PM  
CHEMIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-223/S004**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

14 Feb. 2003

Review for HFD 510

**NDA:** 21-223/SCF004-BZ

**Drug Product Name**

**Proprietary:** Zometa®  
**Non-proprietary:** zoledronic acid for injection

**Drug Product Classification:** 3

**Review Number:** 2

**Subject of this Review**

**Submission Date:** November 6, 2002  
**Receipt Date:** November 7, 2002  
**Consult Date:** February 13, 2003  
**Date Assigned for Review:** February 13, 2003

**Submission History (for amendments only)**

**Date(s) of Previous Submission(s):** June 20, 2002  
**Date(s) of Previous Micro Review(s):** October 8, 2002

**Applicant/Sponsor**

**Name:** Novartis Pharmaceuticals Corporation  
**Address:** One Health Plaza  
East Hanover, NJ 07936-1080

**Representative:** Elizabeth McCartney  
**Telephone:** 973-781-8391

**Name of Reviewer:** Stephen E. Langille, Ph.D.

**Conclusion:** The submission is recommended for approval

---

## Product Quality Microbiology Data Sheet

- A.
1. TYPE OF SUPPLEMENT: Prior Approval
  2. SUPPLEMENT PROVIDES FOR: Alternate Formulation
  3. MANUFACTURING SITE: Novartis Pharma Stein AG  
Schaffhauserstrasse  
CH-4332-Stein  
Switzerland
  4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:
    - Injection
    - Intravenous infusion
    - 4 mg
  5. METHOD(S) OF STERILIZATION: \_\_\_\_\_
  6. PHARMACOLOGICAL CATEGORY: Treatment for  
Hypercalcemia  
of Malignancy
- B. SUPPORTING/RELATED DOCUMENTS: DMF \_\_\_\_\_
- C. REMARKS: This review was entered in DFS as a "memo to file" attached to the first microbiology review.

filename: C:\reviews\21-223scf004r2.doc

2 Page(s) Withheld

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       § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Withheld Track Number: Microbiology-21-223  
50041

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/s/

-----  
Stephen Langille  
2/19/03 10:39:18 AM  
MICROBIOLOGIST

Peter Cooney  
2/19/03 01:15:11 PM  
MICROBIOLOGIST

# Product Quality Microbiology Review

30 Sept. 2002

Review for HFD 510

**NDA:** 21-223/SCF004

**Drug Product Name**

**Proprietary:** Zometa®  
**Non-proprietary:** zoledronic acid for injection

**Drug Product Classification:** S

**Review Number:** 1

**Subject of this Review**

**Submission Date:** June 20, 2002  
**Receipt Date:** June 21, 2002  
**Consult Date:** July 1, 2002  
**Date Assigned for Review:** July 19, 2002

**Submission History (for amendments only)**

**Date(s) of Previous Submission(s):**  
**Date(s) of Previous Micro Review(s):**

**Applicant/Sponsor**

**Name:** Novartis Pharmaceuticals Corporation  
**Address:** One Health Plaza  
East Hanover, NJ 07936-1080

**Representative:** E.R. McCartney  
**Telephone:** 973-781-8391

**Name of Reviewer:** Stephen E. Langille, Ph.D.

**Conclusion:** The submission is approvable pending the resolution of microbiological deficiencies.



---

## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability -**  
The submission is approvable pending the resolution of microbiological deficiencies.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable -**

### **II. Summary of Microbiology Assessments**

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –**  
The presentation of ZOMETA will be changed from a lyophilized product for reconstitution to a ready-to-use liquid product. It will  

---

Novartis Pharma AG in Stein, Switzerland. The facility was inspected by the FDA in June 2001 and March 2002.
- B. Brief Description of Microbiology Deficiencies -**  
The Applicant did not clearly define their policy for reprocessing the drug product in the 

---
- C. Assessment of Risk Due to Microbiology Deficiencies -**  
If the drug product is to be re-processed, additional testing may be required to insure that the container integrity has not been compromised.

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_
- B. Endorsement Block**  
In DFS
- C. CC Block**  
In DFS

6 Page(s) Withheld

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§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

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/s/

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Stephen Langille  
10/8/02 03:20:50 PM  
MICROBIOLOGIST

Peter Cooney  
10/8/02 03:24:41 PM  
MICROBIOLOGIST

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-223/S004**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**Division of Metabolic and Endocrine Drug Products**

**PROJECT MANAGER LABELING REVIEW**

**Application Number:** 21-223/S-004

**Name of Drug:** Zometa (zoledronic acid) Injection

**Sponsor:** Novartis Pharmaceuticals Corporation

**Material Reviewed**

**Submission Dates:**

- February 10, 2003, submission containing a draft package insert, and carton and vial labels.

**Background and Summary Description:**

The supplemental NDA was submitted on June 20, 2002. Zometa is currently approved as a lyophilized powder for injection to treat hypercalcemia of malignancy, and the supplement provides for a solution dosage form of the drug product. We sent the firm an approvable letter October 18, 2002, and the firm submitted a complete response to the approvable letter on November 6, 2002.

**Review**

Vial

The submitted draft vial label (Identifier Number 85054701, No Revised Date) submitted February 10, 2003 was compared to the Final Printed labeling (FPL) for the approved product vial label (Identifier Number 85021203, No Revised Date) acknowledged and retained August 29, 2002. The NDC number of the vial label is different and the name is changed from Zometa (zoledronic acid) ~~Injection~~ to Zometa (zoledronic acid) Injection.

Carton

The submitted draft carton (Identifier Number 83033501, No Revised Date) submitted February 10, 2003 was compared to the FPL for the approved product carton (Identifier Number 83012104, No Revised Date) acknowledged and



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/s/

-----  
Randy Hedin  
3/7/03 09:22:42 AM  
CSO

**From:** Hedin, Durand M  
**Sent:** Monday, March 03, 2003 2:48 PM  
**To:** 'Elizabeth.McCartney@Pharma.Novartis.com'  
**Subject:** NDA 21-223/S-004

Dear Ms. McCartney:

Please refer to your June 20, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid) Injection.

We also refer to your amendment dated October 1, 2002.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following information requests. We request a prompt response in order to continue our evaluation of your supplemental new drug application.

The following questions concern your October 1, 2002 submission.

- Attachment 1: Supportive stability report / \_\_\_\_\_  
Concerning the sample chromatogram after \_\_\_\_\_
  1. Why is there no peak of the \_\_\_\_\_
  2. Please also provide chromatograms of the \_\_\_\_\_
- Attachment 3: Stability commitment report / \_\_\_\_\_  
Concerning the sample chromatogram after \_\_\_\_\_  
(pg. 38):
  1. Why is there no peak of the \_\_\_\_\_
  2. Please also provide chromatograms of the \_\_\_\_\_
- In addition, indicate the \_\_\_\_\_ for the chromatograms obtained with \_\_\_\_\_ 1.

Sincerely,

Randy Hedin

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/s/

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Randy Hedin  
3/3/03 03:44:05 PM  
CSO



NDA 21-223/S-004

**INFORMATION REQUEST LETTER**

Novartis Pharmaceuticals Corporation  
Attention: Elizabeth McCartney  
Assistant Director, Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

Please refer to your June 20, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We also refer to your submission dated January 10, 2003,

Further, we refer to a teleconference between you, Mr. Randy Hedin and myself on January 30, 2003. In the teleconference it was agreed that the name Zometa (zoledronic acid) Injection would be used for the name of the solution dosage form of your drug product.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

Sheldon Markofsky, Ph.D.  
Acting Chemistry Team Leader II, DNDC II for the  
Division of Metabolic and Endocrine Drug  
Products, HFD-510  
Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Sheldon Markofsky  
1/31/03 11:37:26 AM



NDA 21-223/S-004

## INFORMATION REQUEST LETTER

Novartis Pharmaceuticals Corporation  
Attention: Elizabeth McCartney  
Assistant Director, Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

Please refer to your June 20, 2002 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zometa (zoledronic acid for injection).

We also refer to your submission dated August 26, 2002.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests in response to three questions you posed in your August 26, 2002 submission. Our answers follow your questions. We request a prompt written response in order to continue our evaluation of your supplemental new drug application.

1. Novartis is prepared to amend the stability commitment to provide for extractable testing after 1 months storage at accelerated conditions. The current commitments does not require extractables testing until the 1 months timepoint which will be available in 1 month. Would providing 1 months extractables and stability data prior to the action date be acceptable?

Yes, providing extractable testing data after 1 months storage at accelerated conditions 1 month would be acceptable.

2. Is the Novartis proposal for a 1 day extraction study at accelerated conditions, as outlined in our response to question 3, in line with FDA's request?

Yes, it is in line with FDA's request. Please note that the 1 day extraction study should be done on vials containing the drug product. However, we are not prepared to approve your currently proposed ink because its components and composition have not been specified. All components and composition of the ink and the adhesive should be submitted directly to the NDA, or via the manufacturer in the form of a drug master file. Information on the toxicity of each component and, if possible,

Code of Federal Regulations references for their use and contact with food or drugs would also be helpful.

3. If Novartis were to

~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~  
after 1 months storage at accelerated conditions ~~\_\_\_\_\_~~ In addition, you should provide ~~\_\_\_\_\_~~ extraction study data using labeled vials containing the drug product.

If you have any questions, call Randy Hedin, Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

Sheldon Markofsky, Ph.D.  
Acting Chemistry Team Leader II, DNDC II for the  
Division of Metabolic and Endocrine Drug  
Products, HFD-510  
Office of New Drug Chemistry  
Center for Drug Evaluation and Research

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/s/

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Sheldon Markofsky  
9/13/02 09:45:54 AM



NDA 21-223/S-004

**PRIOR APPROVAL SUPPLEMENT**

Novartis Pharmaceuticals Corporation  
Attention: Elizabeth McCartney  
Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. McCartney:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zometa (zoledronic acid for injection)

NDA Number: 21-223

Supplement Number: S-004

Date of Supplement: June 20, 2002

Date of Receipt: June 21, 2002

This supplement proposes a liquid dosage form of the current lyophilized powder for reconstitution.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 20, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 21, 2002.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows.

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic and Endocrine Drug Products, HFD-510  
Attention: Division Document Room 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

Randy Hedin, R.Ph.  
Senior Regulatory Management Officer  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

-----  
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/s/

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Randy Hedin

7/2/02 09:39:54 AM

## Memorandum to File

**To:** NDA 21-223/S-004

**From:** E. Chikhale, Ph.D. – Chemistry Reviewer

**Subject:** Response to general Correspondence - CMC, dated 1-10-2003

**Date:** January 27, 2003

In a general correspondence – CMC dated 1-10-2003, the applicant proposes to use the proprietary name of Zometa

the applicant proposes to

This approach is not acceptable

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/s/

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Elsbeth Chikhale  
1/28/03 01:47:40 PM  
CHEMIST

Sheldon Markofsky  
1/29/03 08:50:00 AM  
CHEMIST

MEMO TO FILE

Regarding 21-223/SCF-004

Feedback from FDA to questions Novartis presented in Attachment 2 of their communication dated 8-26-02:

1. Yes, providing ~~4~~ month extractables and stability data (accelerated conditions  ~~/                      /~~ would be acceptable.
2. Yes, it is in line with FDA's request. Please note that the  ~~/~~ extraction study should be done on vials containing the drug product. However, we are not prepared to approve your currently proposed ink because its components and composition have not been specified. All components and composition of the ink and the adhesive should be submitted directly to the NDA or via the manufacturer in the form of a DMF. Information on the toxicity of each component and, if possible, CFR references for their use and contact with food or drugs would also be helpful.
3. We would require,  ~~/                      /~~ full information regarding the components and composition of the ink and adhesive, in addition to ~~4~~ month extractables and stability data (accelerated conditions  ~~/                      /~~ and  ~~/                      /~~ extraction study data using vials containing the drug product.

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/s/

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Elsbeth Chikhale  
9/12/02 09:53:44 AM  
CHEMIST

Sheldon Markofsky  
9/12/02 10:21:06 AM  
CHEMIST

**From:** Hedin, Durand M  
**Sent:** Monday, November 18, 2002 1:16 PM  
**To:** Phillips, Jerry  
**Cc:** Orloff, David G; Markofsky, Sheldon B; Chikhale, Elsbeth G  
**Subject:** RE: Correspondence (11/8/02) to ODS concerning Zometa

Jerry,  
Good point. However, in the case sited / \_\_\_\_\_  
/ \_\_\_\_\_ In the case of Zometa, if Novartis wishes to use the tradenames  
/ \_\_\_\_\_ that would be fine also. But to use only the name  
Zometa to refer to / \_\_\_\_\_

Randy

-----Original Message-----

**From:** Phillips, Jerry  
**Sent:** Monday, November 18, 2002 1:06 PM  
**To:** Hedin, Durand M  
**Subject:** RE: Correspondence (11/8/02) to ODS concerning Zometa

Randy:

I would disagree with that approach. The physician will probably only need to write for

directions are conveyed in the Rx. / \_\_\_\_\_

Jerry

-----Original Message-----

**From:** Hedin, Durand M  
**Sent:** Monday, November 18, 2002 1:00 PM  
**To:** Phillips, Jerry  
**Cc:** Orloff, David G; Markofsky, Sheldon B; Chikhale, Elsbeth G  
**Subject:** RE: Correspondence (11/8/02) to ODS concerning Zometa

Hi Jerry,

It was our opinion that it is / \_\_\_\_\_

I hope this is helpful, If you have any questions contact me.

Thanks,

Randy

-----Original Message-----

**From:** Phillips, Jerry  
**Sent:** Saturday, November 16, 2002 11:38 AM  
**To:** Orloff, David G  
**Cc:** Hedin, Durand M; Markofsky, Sheldon B; Raczkowski, Victor F  
**Subject:** Correspondence (11/8/02) to ODS concerning Zometa

David:

ODS (Victor Raczowski) received correspondence on November 8, 2002 from Novartis concerning NDA 21-223/S-004 for a new concentrate for infusion of Zometa. The firm had proposed to use the same proprietary name of Zometa. /

/ has no record of receiving a consult from the Division to review this proposal, we agree with Novartis that developing a /

the Division of Medication Errors and Technical Support and CDER's position of / Our recommendation would be /

/ If necessary, I would be willing to meet with you to discuss the issue.

Thanks.

Jerry Phillips  
Associate Director, ODS  
7-7845

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/s/

-----  
Randy Hedin  
11/18/02 04:12:06 PM  
CSO

## REQUEST FOR CONSULTATION

TO (Division/Office) HFD-160 Attn: Peter Cooney FROM: HFD-510

DATE July 1, 2002	IND NO.	NDA NO. 21-223	TYPE OF DOCUMENT Supplement	DATE OF DOCUMENT June 20, 2002
----------------------	---------	-------------------	--------------------------------	-----------------------------------

NAME OF DRUG Zometa (zoledronic acid for inj.)	PRIORITY CONSIDERATION S	CLASSIFICATION OF DRUG 1	DESIRED COMPLETION DATE September 1, 2002
---	-----------------------------	-----------------------------	--

NAME OF FIRM Novartis Pharmaceuticals Corp.

**REASON FOR REQUEST**

**I. GENERAL**

- |  |  |   |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW) |
|--|--|---|

**II. BIOMETRICS**

<b>STATISTICAL EVALUATION BRANCH</b> <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER	<b>STATISTICAL APPLICATION BRANCH</b> <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER
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**III. BIOPHARMACEUTICS**

- |   |  |
|---|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

**IV. DRUG EXPERIENCE**

- |  |   |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

**V. SCIENTIFIC INVESTIGATIONS**

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: Please review sterility issues in the attached supplement (See pages 778 through 842). The first (administrative) volume is sent for your convenience.

Dr. Elsbeth Chikhale is the chemist, 827-6396.  
Mr. Randy Hedin is the CSO, 827-6392.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> X MAIL <span style="float: right;">HAND</span>
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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
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Randy Hedin

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Randy Hedin  
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